General

Guideline Title

Alemtuzumab for treating relapsing–remitting multiple sclerosis.

Bibliographic Source(s)

National Institute for Health and Care Excellence (NICE). Alemtuzumab for treating relapsingâ€“remitting multiple sclerosis. London (UK): National Institute for Health and Care Excellence (NICE); 2014 May. 58 p. (Technology appraisal guidance; no. 312).

Guideline Status

This is the current release of the guideline.

Recommendations

Major Recommendations

Alemtuzumab is recommended as an option, within its marketing authorisation, for treating adults with active relapsing–remitting multiple sclerosis (RRMS).

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Relapsing–remitting multiple sclerosis (RRMS)

Guideline Category

Assessment of Therapeutic Effectiveness

Treatment

Clinical Specialty

Family Practice

Internal Medicine

Neurology

Intended Users

Advanced Practice Nurses

Nurses

Physician Assistants

Physicians

Guideline Objective(s)

To assess the clinical effectiveness and cost-effectiveness of alemtuzumab for the treatment of relapsing-remitting multiple sclerosis (RRMS)

Target Population

Adult patients with active relapsing–remitting multiple sclerosis

Interventions and Practices Considered

Alemtuzumab

Major Outcomes Considered

- Clinical effectiveness
  - Relapse rate
  - Severity of relapse
  - Disability rate
  - Symptoms
  - Freedom from disease activity
  - Mortality
  - Adverse events of treatment
  - Health-related quality of life
  - Hospitalisation rate
- Cost-effectiveness

Methodology

Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

Searches of Unpublished Data

Description of Methods Used to Collect/Select the Evidence

Note from the National Guideline Clearinghouse (NGC): The National Institute for Health and Care Excellence (NICE) commissioned an independent academic centre to perform an assessment of the manufacturer's submission on the technology considered in this appraisal and prepare an Evidence Review Group (ERG) report. The ERG report for this technology appraisal was prepared by Southampton Health Technology Assessment Centre (see the "Availability of Companion Documents" field).

Clinical Effectiveness

Description of Manufacturer's Search Strategy

The Genzyme manufacturer's submission (GMS) search strategies are considered overall to be of a reasonable quality, with a few minor inconsistencies. There is a mix of free text and descriptors that have been correctly combined into sets on appropriate databases. The PICO (participants, intervention, comparator, outcomes) breakdown within the search strategy line numbers throughout the GMS was considered to be useful. There is some slight variance in the text and appendices of reporting the dates the searches were undertaken.

The GMS accessed Medline and Medline-R through PubMed for the clinical searches and via EMBASE for all other searches. The GMS did not report the number of return hits per line number in the searches for clinical effectiveness, but did for the other searches. The use of the same platform for all the searches would have been a more consistent approach.

The ERG uses Ovid as a search interface and this employs a slightly different syntax; however, the search strategies appear to be appropriate. There were some differences in the terms used to represent the intervention and comparator elements of the clinical searches and the cost related searches. The GMS has elected to use a highly specific randomised controlled trial (RCT) filter in the clinical searches, although the results on testing with a more sensitive RCT filter appeared not to produce additional significant results.

The searches were not updated prior to submission and the ERG has therefore updated the clinical and cost-effectiveness searches up to end July 2013. There did not appear to be a systematic search for ongoing studies. The ERG ran searches on the United Kingdom Clinical Research Network (UKCRN), Current Controlled Trials, clinicaltrials.gov, and the World Health Organization International Clinical Trials Registry Platform (WHO ICTRP).

The GMS does not report a separate search to identify adverse drug reactions. This appears a reasonable approach as the ERG considers that adverse event search filters are of questionable value and that side effects are not always reported in abstracts on bibliographic databases. Safety data were pooled from the main trials, CAMMS223, CARE-MS I, CARE-MS II, and a trial extension (CAMMS03409), and from the manufacturer's safety update reviews.

A reasonable range of grey literature has been searched to identify conference abstracts throughout the GMS and hand searching has also been reported. The quality of life searches use an acceptable filter with restrictions to the UK on one platform but not on the NHS Economic Evaluation Database (NHSEED), which appears reasonable. The natural history epidemiology searches and the mortality searches appear appropriate with a range of grey literature searched.

Statement of the Inclusion/Exclusion Criteria Used in the Study Selection

The inclusion and exclusion criteria are clearly stated in the GMS. This appears to be relevant to the clinical effectiveness review and the mixed treatment comparison (MTC). The GMS stated that the focus in the decision problem was on 'active' relapsing-remitting multiple sclerosis (RRMS); however, in the inclusion criteria this is not stated as such, text states 'adult patients with RRMS'.

Single or double blind RCTs and open label extensions of RCTs were eligible for inclusion. No limits for inclusion were placed on eligibility relating to study quality and setting was not used as an inclusion criterion, but this does not appear to be a relevant factor.

See Section 3 of the ERG report for additional details regarding the manufacturer's search strategy (see the "Availability of Companion Documents" field).

Economic Evaluation

Manufacturer's Review of Published Economic Evaluations

A systematic search of the literature was conducted by the manufacturer to identify economic evaluations of adults with RRMS or progressive MS (including secondary progressive MS [SPMS] or progressive-relapsing MS [PRMS]). The review identified 33 studies evaluating cost-effectiveness in MS, although none of these studies were of alemtuzumab.

Number of Source Documents

Clinical Effectiveness

The literature review identified 2004 potential trials, of which 52 trials were eligible for qualitative synthesis. Of these, three randomised controlled trials (RCTs) included alemtuzumab as a treatment, two trials in treatment-naïve and one trial in treatment-experienced patients. In addition, evidence from two extension studies from the included trials was presented. The manufacturer's submission also included two non-RCTs, chosen without a systematic search and not incorporated into a systematic review; a meta-analysis of the RCTs included in the direct comparison; and a mixed treatment comparison (MTC) based on the literature review for the head-to-head trials.

Cost-Effectiveness

The review identified 33 studies evaluating cost-effectiveness in multiple sclerosis, although none of these studies were of alemtuzumab. The manufacturer submitted a cost-effectiveness analysis of alemtuzumab compared with beta-interferons, glatiramer acetate, fingolimod and natalizumab for active relapsing-remitting multiple sclerosis (RRMS).

Methods Used to Assess the Quality and Strength of the Evidence

Expert Consensus

Rating Scheme for the Strength of the Evidence

Not applicable

Methods Used to Analyze the Evidence

Meta-Analysis

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

Note from the National Guideline Clearinghouse (NGC): The National Institute for Health and Care Excellence (NICE) commissioned an independent academic centre to perform an assessment of the manufacturer's submission on the technology considered in this appraisal and prepare an Evidence Review Group (ERG) report. The ERG report for this technology appraisal was prepared by Southampton Health Technology Assessment Centre (see the "Availability of Companion Documents" field).

Clinical Effectiveness

Statement of Manufacturer's Approach to Evidence Synthesis

The ERG assessed the quality of the Genzyme manufacturer's submission (GMS) based on Centre for Reviews and Dissemination (CRD) questions for a systematic review and a summary of the overall quality of the submission can be seen in Table 7 in the ERG report.

The processes for inclusion/exclusion and data extraction were reported in the GMS and were assessed as being adequate by the ERG. There is less detail provided for the processes of undertaking the quality assessment. The majority of the information about the processes for the inclusion/exclusion and data extraction was found in the appendices rather than the main submission.

The ERG considers the submitted evidence to partly reflect the defined decision problem in the GMS. The main issue is the relation of the

populations in the included trials to the scoped population of people with relapsing-remitting multiple sclerosis (RRMS), in particular with respect to the scoped subgroups.

Overall the chance of any systematic error in the systematic review based on the methods employed is uncertain.

Summary of Submitted Evidence

The ERG has reproduced data for the key outcomes from the included trials, the direct meta-analysis results and the mixed treatment comparison (MTC). For some of the outcomes (including the pooled data) the GMS report these as relative risk (RR) and the ERG have followed this convention. However, on checking the data inputs it would appear that for some outcomes (proportion relapse free and discontinuations) odds ratios were used, and for others (annualised relapse rate [ARR] and sustained accumulation of disability [SAD]) hazard ratios were used.

See Section 3 of the ERG report for additional details (see the "Availability of Companion Documents" field).

Economic Evaluation

Critical Appraisal of Manufacturer's Submitted Economic Evaluation

The ERG have considered the methods applied in the economic evaluation in the context of the critical appraisal questions listed in Table 26 in the ERG report, drawn from common checklists for economic evaluation methods. The critical appraisal checklist indicates that overall the manufacturer follows recommended methodological guidelines.

Modelling Approach/Model Structure

The GMS economic model consisted of a multi-state Markov model with health states for Expanded Disability Status Scale (EDSS), secondary progressive multiple sclerosis (SPMS), and death (see Figure 1 in the ERG report [see the "Availability of Companion Documents" field]). Costs and quality adjusted life year (QALYs) were calculated over a life time horizon (50 years) and discounted at 3.5% per annum. Cost categories were based on the National Health Service (NHS) and personal social services (PSS) perspective.

Patients enter the model in one of ten EDSS health states. In each annual cycle, active RRMS patients may remain in the same EDSS state, progress to a more severe EDSS state, convert to SPMS or die. Once a patient converts to SPMS, they may remain in the same EDSS state, progress to a more severe EDSS state or die. Death is represented by EDSS 10. The model also estimates the frequency of relapses leading to hospitalisation and not leading to hospitalisation.

The GMS uses two approaches to measure disease progression in the model. The first approach applied hazards ratios (HRs), derived from a MTC, to a natural history dataset. This approach is used for the comparative analysis for all treatments and is referred to in the GMS as the "natural history comparison".

The second approach used transition probabilities derived directly from patient level data of the two alemtuzumab trials (CARE-MS I and CARE-MS II). This method was used for a sensitivity analysis comparison between alemtuzumab and interferon (IFN)β-1a 44 µg. This method is referred to as "direct comparison".

See Section of the ERG report for additional information on the cost-effectiveness analysis (see the "Availability of Companion Documents" field).

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

Considerations

Technology appraisal recommendations are based on a review of clinical and economic evidence.

Technology Appraisal Process

The National Institute for Health and Care Excellence (NICE) invites 'consultee' and 'commentator' organisations to take part in the appraisal process. Consultee organisations include national groups representing patients and carers, the bodies representing health professionals, and the manufacturers of the technology under review. Consultees are invited to submit evidence during the appraisal and to comment on the appraisal

documents.

Commentator organisations include manufacturers of the products with which the technology is being compared, the National Health Service (NHS) Quality Improvement Scotland and research groups working in the area. They can comment on the evidence and other documents but are not asked to submit evidence themselves.

NICE then commissions an independent academic centre to review published evidence on the technology and prepare an 'assessment report'. Consultees and commentators are invited to comment on the report. The assessment report and the comments on it are then drawn together in a document called the evaluation report.

An independent Appraisal Committee then considers the evaluation report. It holds a meeting where it hears direct, spoken evidence from nominated clinical experts, patients and carers. The Committee uses all the evidence to make its first recommendations, in a document called the 'appraisal consultation document' (ACD). NICE sends all the consultees and commentators a copy of this document and posts it on the NICE Web site. Further comments are invited from everyone taking part.

When the Committee meets again it considers any comments submitted on the ACD; then it prepares its final recommendations in a document called the 'final appraisal determination' (FAD). This is submitted to NICE for approval.

Consultees have a chance to appeal against the final recommendations in the FAD. If there are no appeals, the final recommendations become the basis of the guidance that NICE issues.

Who Is on the Appraisal Committee?

NICE technology appraisal recommendations are prepared by an independent committee. This includes health professionals working in the NHS and people who are familiar with the issues affecting patients and carers. Although the Appraisal Committee seeks the views of organisations representing health professionals, patients, carers, manufacturers and government, its advice is independent of any vested interests.

Rating Scheme for the Strength of the Recommendations

Not applicable

Cost Analysis

Summary of Appraisal Committee's Key Conclusions on the Evidence for Cost-effectiveness

Availability and Nature of Evidence

The Committee considered the manufacturer's revised base-case results submitted in response to consultation. It was aware the manufacturer had incorporated all the Committee's preferred assumptions.

Uncertainties Around and Plausibility of Assumptions and Inputs in the Economic Model

The Committee heard that the alemtuzumab trial data and other evidence suggested that people's Expanded Disability Status Scale (EDSS) states could improve and concluded that it is appropriate for the economic modelling to allow patients to move to lower as well as to higher EDSS states.

The Committee considered that the trials provided the most appropriate source of quality of life data because the trial population best reflects the population that would receive the treatment in clinical practice. A number of deaths were observed in the trials and this needed to be reflected in the economic modelling.

The clinical specialists also commented that the long-term benefit of alemtuzumab is unknown given the absence of long-term data, but that it would be reasonable to assume that alemtuzumab's treatment effect might start to decrease between 3 and 5 years after treatment.

In the trials a further cycle of alemtuzumab was offered to patients if a relapse that lasted for at least 24 hours occurred after the second annual course of infusions, and the clinical specialists commented that further treatments were considered likely in clinical practice. The Committee concluded that it is appropriate to incorporate the time-dependent rate of retreatment in the model.

The Committee concluded that it was more appropriate to remove the mid-cycle correction for the cost of alemtuzumab treatment, increase the number of monitoring and neurology visits to reflect any additional monitoring needed, only include health states costs that are likely to meet the National Institute for Health and Care Excellence (NICE) reference case and to include the costs associated with managing adverse effects in the

economic modelling.

The Committee agreed that it was more appropriate for the manufacturer to use trial data to determine the initial EDSS distribution because this was representative of the patient population likely to be treated with alemtuzumab in the United Kingdom (UK). The Committee was also aware that the manufacturer of alemtuzumab has collected data in patients randomised to placebo and concluded that this dataset would more accurately reflect the natural history of disease in people who would be treated with alemtuzumab in the UK.

Incorporation of Health-related Quality-of-Life Benefits and Utility Values. Have Any Potential Significant and Substantial Health-related Benefits Been Identified That Were Not Included in the Economic Model, and How Have They Been Considered?

The manufacturer pooled EuroQoL-5 Dimension-5 Level (EQ-5D-5L) utility scores by EDSS state from CARE-MS I and CARE-MS II.

The Committee noted that alemtuzumab did provide a step change in the treatment of active relapsing–remitting multiple sclerosis. However, these benefits would already be captured through increased efficacy gains, both in survival gains and in quality of life gains.

Are There Specific Groups of People for Whom the Technology Is Particularly Cost-Effective?

n/a

What Are the Key Drivers of Cost-effectiveness?

The manufacturer's original assumption that the treatment effect from alemtuzumab would persist for many years after the last treatment. The Committee was satisfied that the manufacturer's revised economic analyses adequately explored the sensitivity of the incremental cost-effectiveness ratio (ICER) to several scenarios assuming that the effectiveness of alemtuzumab and its comparators waned over time.

Most Likely Cost-effectiveness Estimate (Given as an ICER)

The Committee concluded that the most plausible ICER for alemtuzumab compared with glatiramer acetate for people with active relapsing-remitting multiple sclerosis is likely to lie between £13,600 and £24,500 per quality adjusted life year (QALY) gained.

The Committee noted that the most plausible ICER for patients with highly active relapsing-remitting multiple sclerosis despite beta interferon treatment was £8900 per QALY gained for alemtuzumab compared with fingolimod. The Committee noted that for patients with rapidly evolving severe relapsing-remitting multiple sclerosis, alemtuzumab dominated natalizumab (that is, less expensive and more effective).

Method of Guideline Validation

External Peer Review

Description of Method of Guideline Validation

Consultee organisations from the following groups were invited to comment on the draft scope, Assessment Report and the Appraisal Consultation Document (ACD) and were provided with the opportunity to appeal against the Final Appraisal Determination.

- Manufacturer/sponsors
- Professional/specialist and patient/carer groups
- Commentator organisations (without the right of appeal)

In addition, individuals selected from clinical expert and patient advocate nominations from the professional/specialist and patient/carer groups were also invited to comment on the ACD.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of evidence supporting the recommendations is not specifically stated.

The Appraisal Committee considered clinical and cost-effectiveness evidence submitted by the manufacturer of alemtuzumab and a review of this submission by the Evidence Review Group. The manufacturer provided clinical-effectiveness evidence, identified by systematic review, from 2 phase III randomised controlled clinical trials, 1 phase II randomised controlled clinical trial, and 1 extension study. In addition, the manufacturer submitted a meta-analysis of the above-listed trials and a mixed-treatment comparison to compare alemtuzumab with other disease-modifying treatments for active relapsing–remitting multiple sclerosis. For cost-effectiveness, the manufacturer submitted an economic model.

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Appropriate use of alemtuzumab for treating relapsing–remitting multiple sclerosis (RRMS)

Potential Harms

The summary of product characteristics lists the following adverse reactions for alemtuzumab: autoimmunity (immune thrombocytopenic purpura, thyroid disorders, nephropathies [kidney diseases or damage], cytopenias [reduced blood cell numbers]), infusion-associated reactions, rash, headache, fever and respiratory tract infections. For full details of adverse reactions, see the summary of product characteristics.

Contraindications

Contraindications

For full details of contraindications, see the summary of product characteristics.

Qualifying Statements

Qualifying Statements

- This guidance represents the views of the National Institute for Health and Care Excellence (NICE) and was arrived at after careful consideration of the evidence available. Healthcare professionals are expected to take it fully into account when exercising their clinical judgement. However, the guidance does not override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.
- Implementation of this guidance is the responsibility of local commissioners and/or providers. Commissioners and providers are reminded that it is their responsibility to implement the guidance, in their local context, in light of their duties to have due regard to the need to eliminate unlawful discrimination, advance equality of opportunity and foster good relations. Nothing in this guidance should be interpreted in a way that would be inconsistent with compliance with those duties.

Implementation of the Guideline

Description of Implementation Strategy

- Section 7(6) of the National Institute for Health and Care Excellence (NICE) (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires clinical commissioning groups, the National Health Service (NHS) England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.
- When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraph

above. This means that, if a patient has active relapsing–remitting multiple sclerosis and the doctor responsible for their care thinks that alemtuzumab is the right treatment, it should be available for use, in line with NICE's recommendations.

- NICE has developed a costing template and report to estimate the national and local savings and costs associated with implementation. These are available on the NICE Web site (see the "Availability of Companion Documents" field).

Implementation Tools

Mobile Device Resources

Patient Resources

Resources

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Living with Illness

IOM Domain

Effectiveness

Patient-centeredness

Identifying Information and Availability

Bibliographic Source(s)

National Institute for Health and Care Excellence (NICE). Alemtuzumab for treating relapsingâ€“remitting multiple sclerosis. London (UK): National Institute for Health and Care Excellence (NICE); 2014 May. 58 p. (Technology appraisal guidance; no. 312).

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2014 May

Guideline Developer(s)

National Institute for Health and Care Excellence (NICE) - National Government Agency [Non-U.S.]

Source(s) of Funding

National Institute for Health and Care Excellence (NICE)

Guideline Committee

Appraisal Committee

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Financial Disclosures/Conflicts of Interest

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

Guideline Status

This is the current release of the guideline.

Guideline Availability

Electronic copies: Available from the National Institute for Health and Care Excellence (NICE) Web site .

Availability of Companion Documents

The following are available:

- Alemtuzumab for treating relapsing–remitting multiple sclerosis. Costing template. London (UK): National Institute for Health and Care Excellence (NICE); 2014 May. (Technology appraisal guidance; no. 312). Electronic copies: Available from the National Institute for

Health and Care Excellence (NICE) Web site.

- Alemtuzumab for treating relapsing–remitting multiple sclerosis. Costing report. London (UK): National Institute for Health and Care Excellence (NICE); 2014 May. 10 p. (Technology appraisal guidance; no. 312). Electronic copies: Available from the NICE Web site.
- Cooper, K, Bryant J, Harris P, Loveman E, Jones J, Welch K. Alemtuzumab for the treatment of relapsing-remitting multiple sclerosis: a single technology appraisal. Southampton (UK): Southampton Health Technology Assessments Centre (SHTAC); 2013 Sep. 88 p. Electronic copies: Available from the NICE Web site.

Patient Resources

The following is available:

- Alemtuzumab for treating active relapsingâ€'remitting multiple sclerosis. Information for the public. London (UK): National Institute for Health and Care Excellence (NICE); 2014 May. (Technology appraisal guidance; no. 312). Electronic copies: Available from the National Institute for Health and Care Excellence (NICE) Web site. Also available for download as a Kindle or EPUB ebook from the NICE Web site.

Please note: This patient information is intended to provide health professionals with information to share with their patients to help them better understand their health and their diagnosed disorders. By providing access to this patient information, it is not the intention of NGC to provide specific medical advice for particular patients. Rather we urge patients and their representatives to review this material and then to consult with a licensed health professional for evaluation of treatment options suitable for them as well as for diagnosis and answers to their personal medical questions. This patient information has been derived and prepared from a guideline for health care professionals included on NGC by the authors or publishers of that original guideline. The patient information is not reviewed by NGC to establish whether or not it accurately reflects the original guideline's content.

NGC Status

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